Cost-Effectiveness of Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease and Abnormal Fractional Flow Reserve

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Background—The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 2 trial demonstrated a significant reduction in subsequent coronary revascularization among patients with stable angina and at least 1 coronary lesion with a fractional flow reserve ≤0.80 who were randomized to percutaneous coronary intervention (PCI) compared with best medical therapy. The economic and quality-of-life implications of PCI in the setting of an abnormal fractional flow reserve are unknown.

Methods and Results—We calculated the cost of the index hospitalization based on initial resource use and follow-up costs based on Medicare reimbursements. We assessed patient utility using the EQ-5D health survey with US weights at baseline and 1 month and projected quality-adjusted life-years assuming a linear decline over 3 years in the 1-month utility improvements. We calculated the incremental cost-effectiveness ratio based on cumulative costs over 12 months. Initial costs were significantly higher for PCI in the setting of an abnormal fractional flow reserve than with medical therapy ($9927 versus $3900, \(P<0.001\)), but the $6027 difference narrowed over 1-year follow-up to $2883 (\(P<0.001\)), mostly because of the cost of subsequent revascularization procedures. Patient utility was improved more at 1 month with PCI than with medical therapy (0.054 versus 0.001 units, \(P<0.001\)). The incremental cost-effectiveness ratio of PCI was $36,000 per quality-adjusted life-year, which was robust in bootstrap replications and in sensitivity analyses.

Conclusions—PCI of coronary lesions with reduced fractional flow reserve improves outcomes and appears economically attractive compared with best medical therapy among patients with stable angina.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01132495.

(Circulation. 2013;128:1335-1340.)

Key Words: coronary disease ■ fractional flow reserve, myocardial ■ percutaneous coronary intervention

The optimal management strategy for patients with stable angina and documented coronary artery disease (CAD) remains controversial. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial randomized patients to percutaneous coronary intervention (PCI) or best medical therapy alone and found that PCI reduced anginal symptoms and improved quality of life at 3 years but did not reduce the rates of death or myocardial infarction.\(^1,2\) The cost-effectiveness of PCI in the COURAGE study was not favorable, however, with an incremental cost-effectiveness ratio (ICER) of ≥$168,000 per quality-adjusted life-year (QALY).\(^3\)

Fractional flow reserve (FFR) measured with a coronary pressure wire during cardiac catheterization can identify functionally important coronary narrowings more accurately than visual assessment of the coronary angiogram.\(^4\) Use of FFR to guide PCI and treat only flow-limiting lesions was shown in the randomized FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial to improve clinical outcomes and to have lower costs than angiography-guided PCI among patients with multivessel CAD.\(^5,6\) Subsequently, the FAME 2 trial randomized patients with stable angina, angiographically documented CAD, and ≥1 lesion with reduced FFR to either PCI or best medical therapy.\(^7\) The FAME 2 study was stopped early based on

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Received April 11, 2013; accepted August 5, 2013.

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.003059

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the recommendation of the Data Safety Monitoring Board because of a significant reduction in the rate of hospitalization for urgent revascularization among patients assigned to PCI in the setting of an abnormal FFR, although the rates of death and myocardial infarction were similar between the 2 groups. In the present study, we sought to evaluate the economic and quality-of-life outcomes in the FAME 2 trial.

Methods

Study Design

The design and major clinical outcomes of the FAME 2 trial have been published previously. Briefly, FAME 2 was a prospective, international, randomized, controlled trial that enrolled patients with stable angina and CAD (1-, 2-, or 3-vessel disease) amenable to PCI with a second-generation drug-eluting stent. Before randomization, FFR was measured across all lesions that appeared significant on visual assessment. Patients with an FFR >0.80 across all lesions were followed up in a registry and not randomized. Significant lesions were randomly assigned to either PCI or to best medical therapy. The FAME 2 study population was therefore limited to patients with documented, significant myocardial ischemia caused by a coronary lesion amenable to PCI. The primary end point was the composite of death, myocardial infarction, or subsequent hospitalization with urgent coronary revascularization.

Costs

We calculated medical costs based on resource use and clinical events during the index procedure, hospitalization, and subsequent follow-up. We counted the number of guiding catheters, coronary guidewires, balloon catheters, stents, medications, adverse events, and hospital days for each patient, as well as time in the cardiac catheterization laboratory, and applied cost weights in US dollars to calculate costs of the index procedure. We assigned costs to postdischarge events based on Medicare’s reimbursement rate per diagnosis-related group (DRG) for hospitalizations, inpatient procedures, outpatient tests, and physician fees and Internet pharmacy costs for cardiac medications. We calculated cumulative costs monthly for 12 months using an actuarial approach and adjusted all costs to 2012 US dollars using the Consumer Price Index (http://www.bls.gov). We did not discount costs because of the limited follow-up period.

Health Outcomes

Angina and employment status were assessed at baseline and at 1, 6, and 12 months. Patient utility was assessed with the EQ-5D health survey with US weights at baseline, 1 month, and 12 months.

Framework of the Economic Evaluation

Analyses were performed from a societal perspective. We assessed the ICER as the difference in the cumulative costs of PCI in the setting of an abnormal FFR and medical therapy, divided by the difference in cumulative QALYs of PCI in the setting of an abnormal FFR and medical therapy. Only 11% of patients provided 12-month EQ-5D scores because the trial was stopped early, so we used the baseline and 1-month EQ-5D data to calculate QALY’s in the 2 treatment groups. On the basis of previous data on the time course of angina relief and quality-of-life changes after coronary revascularization, we assumed that the difference in the improvement from baseline in EQ-5D scores between the randomized groups would decline linearly to zero (ie, to no difference) over 3 years of follow-up. We tested alternative QALY measures, including assumptions that the initial difference in utility would decline linearly to zero over 2 years or over 4 years. We also used an independent approach in which the change in utility from baseline to 1 month was assumed to last through the 12 months of in-trial follow-up in all patients, but follow-up was truncated at 12 months. In this approach, we also assumed patient utility would improve among patients assigned to the medical therapy arm at the time they underwent PCI and that the improvement would last for the remainder of the 12-month follow-up period.

In all analyses, we made the conservative assumption that the difference in cumulative costs at 12 months between the PCI in the setting of an abnormal FFR arm and the medical therapy arm would not change further over subsequent follow-up. We performed sensitivity analyses to assess the impact of different costs of coronary stents and by setting to zero the cost of the coronary pressure wire, the catheterization procedure, and the baseline hospital stay in the medical therapy arm.

Statistical Analysis

We report categorical data as frequencies and continuous data as means±SD. We compared categorical data using the χ² test and continuous data (costs and QALY’s) using the t test. Comparisons between baseline and 1-month utilities were made by the paired t test, whereas comparisons of differences between groups were made by the 2-sample t test. We computed confidence intervals for differences in costs and QALYs and in the ICER using the bootstrap technique with the percentile method with 10,000 replications.

Results

The FAME 2 trial was stopped after 888 patients had been randomized, with a median follow-up of 208 days (first, third quartiles, 103–312 days) in the PCI arm and 209 days (first, third quartiles, 106–314 days) in the medical therapy arm. The baseline characteristics were similar between the 2 groups (Table 1). The primary composite end point of death, myocardial infarction, and urgent revascularization occurred in 4.3% of the 447 patients randomized to PCI in the setting of an abnormal FFR and in 12.7% of the 441 patients randomized to medical therapy (P<0.001). There was no difference in the rate of death (0.2% versus 0.7%, P=0.31) or myocardial infarction (3.4% versus 3.2%, P=0.89), but there was a highly significant difference in the rate of urgent revascularization (1.6% versus 11.1%, P<0.001).

The initial procedure and hospitalization cost was significantly greater among patients randomized to PCI than among

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FFR-Guided PCI (n=447)</th>
<th>Medical Therapy (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.5±9.4</td>
<td>63.9±9.6</td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Previous MI</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>CCS class II or greater angina</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Angiographically significant lesions (number per patient)</td>
<td>1.9±1.1</td>
<td>1.7±0.9</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society; FFR, fractional flow reserve; MI, myocardial infarction; and PCI, percutaneous coronary intervention. Values are percentages or mean±SD.
patients randomized to medical therapy ($9927 versus $3900, \( P<0.001; \) Figure 1). The $6027 initial cost difference was driven primarily by the cost of the PCI procedure (Table 2). Over the subsequent year, follow-up costs were higher in the medical therapy arm, such that the cumulative costs at 12 months were $12,646 in the PCI arm compared with $9763 in the medical therapy arm (\( P<0.001 \)). The higher follow-up costs in the medical therapy arm were driven primarily by the higher rate of revascularization (Table 3). The higher cost of antiplatelet therapy in the PCI arm was balanced by the higher cost of antianginal agents in the medical therapy arm (Table 3).

At 30 days, significantly fewer patients in the PCI arm had Canadian Cardiovascular Society class 2 or greater angina (11.1% versus 28.9%, \( P<0.0001 \)) than those receiving medical therapy alone. The change in patient utility from baseline to 30 days was significantly greater in the PCI arm than in the medical therapy arm (0.054 versus 0.001, \( P<0.0001 \); Table 4). In the 11% of patients who achieved 1-year follow-up, there was a nonsignificant 0.02 decline in utility from 1 to 12 months in both groups. There was little effect of either therapy on employment, with a −3.8% net change in work status among patients assigned to PCI (\( P=0.38 \)), and a −4.4% net change in work status among patients assigned to medical therapy (\( P=0.18 \)) between baseline and 6 months.

Assuming that the effect of PCI on utility would decline linearly over 3 years and that the cost difference present at 1 year would not change, the ICER for PCI compared with medical therapy was $36,000/QALY. The ICER was below a willingness-to-pay threshold of $50,000/QALY in most (80%) of the 10,000 bootstrap replications and was below the $100,000/QALY threshold in almost all (99.5%) replications (Figures 2 and 3).

### Table 2. Resource Use at Initial Procedure

<table>
<thead>
<tr>
<th>Resource (Cost)</th>
<th>FFR-Guided PCI</th>
<th>Medical Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization laboratory</td>
<td>1209</td>
<td>709</td>
</tr>
<tr>
<td>Guide catheter ($52)</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Guidewire ($51)</td>
<td>49</td>
<td>15</td>
</tr>
<tr>
<td>Pressure wire ($650)</td>
<td>650</td>
<td>603</td>
</tr>
<tr>
<td>Balloon catheter ($166)</td>
<td>293</td>
<td>3</td>
</tr>
<tr>
<td>Drug-eluting stent ($1656)</td>
<td>2612</td>
<td>15</td>
</tr>
<tr>
<td>Bare-metal stent ($809)</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Adenosine ($150/vial)</td>
<td>87</td>
<td>67</td>
</tr>
<tr>
<td>GPI ($500/vial)</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Hospital day ($2000)</td>
<td>3067</td>
<td>2018</td>
</tr>
<tr>
<td>Professional fee ($796)</td>
<td>796</td>
<td>0</td>
</tr>
<tr>
<td>Staged PCI</td>
<td>567</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>414</td>
<td>367</td>
</tr>
<tr>
<td>Total baseline costs</td>
<td>9927</td>
<td>3900</td>
</tr>
</tbody>
</table>

| FFR indicates fractional flow reserve; GPI, glycoprotein inhibitor; and PCI, percutaneous coronary intervention. |
Figure 2. Bootstrap replications of the incremental cost-effectiveness of the strategy of percutaneous coronary intervention in the setting of an abnormal fractional flow reserve compared with best medical therapy. Each of the 10,000 points represents the results of 1 bootstrap replication. The difference in cumulative costs is displayed in the vertical axis, and the difference in quality-adjusted life-years (QALYs) is displayed on the horizontal axis. Willingness-to-pay thresholds of $50,000 per QALY added (solid line), $100,000 per QALY added (dashed line), and $150,000 per QALY added (dotted line) are indicated in the plane. The fractions of replications in each sector of the plane are indicated (eg, 0.0023 of the replications had a cost difference <0 and QALY difference >0).

The ICER for PCI was changed in several sensitivity analyses but remained in the $100,000/QALY range or less. When we arbitrarily assumed the cost of a drug-eluting stent was $400 higher than our base case estimate of $165 per stent, the ICER increased to $44,000/QALY, whereas if we assumed the stent cost was $400 lower than the base case, the ICER became $29,000/QALY. When we set the cost of the pressure wire to zero in the medical treatment arm, the ICER became $44,000/QALY. If we assumed the utility benefit of PCI dissipated over 2 years rather than the base case of 3 years, ICER became $54,000/QALY, whereas if we assumed the utility benefit would dissipate over 4 years, the ICER changed to $27,000/QALY. If we set the cost of the nonurgent PCIs in follow-up to zero in the medical treatment arm, the ICER changed to $55,000/QALY. If we limited the follow-up period to 12 months and assumed that medically treated patients after a subsequent PCI had an increase in utility of 0.053, the ICER for PCI became $60,000/QALY. Symptom status did have more of an effect on the ICER; when we analyzed the cost-effectiveness of patients with Canadian Cardiovascular Society class 0/1 angina, it was $102,000/QALY compared with $26,000/QALY in those patients with Canadian Cardiovascular Society class 2 to 4 angina. If Medicare costs were used for the index PCI and there was no change in the baseline costs in the medical therapy arm, the 1-year cost differential would increase by approximately $2000 and the ICER would increase to $63,000/QALY. Finally, if we excluded the baseline cost of the catheterization procedure and hospital stay in the medical therapy arm, the ICER for PCI became $63,000/QALY.

Figure 3. Cost-effectiveness acceptability curve of the incremental cost-effectiveness of the fractional flow reserve-guided strategy compared with best medical therapy, based on 10,000 bootstrap replications. The cumulative percentage of replications (vertical axis) below various willingness-to-pay thresholds (horizontal axis) in dollars per quality-adjusted life-year (QALY) is shown. The points on the curve indicate the cumulative proportion of replications below thresholds of $25,000/QALY (18%), $50,000/QALY (80%), $75,000/QALY (97%), $100,000/QALY (99.5%), $125,000/QALY (99.9%), and $150,000/QALY (99.97%).

Discussion

FFR measured during coronary angiography accurately identifies flow-limiting coronary lesions. The FAME 2 trial demonstrated that PCI of coronary lesions with an FFR ≤0.80 improves clinical outcomes compared with best medical therapy. The present study shows that PCI in the setting of an abnormal FFR also reduces angina and improves patient utility significantly. Although by design the PCI strategy had higher initial costs than the medical therapy strategy, the difference in cost between these strategies was cut by more than half over 1 year of follow-up (Figure 1). PCI in the setting of an abnormal FFR appears to provide good value for the added cost, with an ICER well below the standard willingness to pay threshold of $50,000 per QALY, a finding that was robust in bootstrap replications (Figure 2) and several sensitivity analyses.

The COURAGE trial compared PCI with medical therapy in patients with stable CAD but found PCI to be economically unattractive despite significant improvements in angina and quality of life, with ICERs ranging between $168,000 and $300,000 per QALY.1 By contrast, FAME 2 found an ICER of $36,000 per QALY for PCI in the setting of an abnormal FFR. The most likely explanation for these different results is that PCI in COURAGE was guided by the visual appearance of the lesion on coronary angiography, whereas PCI in FAME 2 was guided by identification of functionally significant lesions based on a measured FFR ≤0.80. The measurement of FFR in FAME 2 excluded 26% of otherwise eligible patients from PCI because they did not have a functionally significant lesion despite having...
angiographically significant CAD. Furthermore, 19% of patients in FAME 2 who had a lesion with an FFR ≤0.80 had another lesion with an FFR >0.80. All of these patients and lesions presumably would have been treated with PCI in COURAGE, with little benefit and perhaps harm because of the absence of significant ischemia. Thus, the targeting of PCI in FAME 2 to the patients and lesions most likely to benefit from it may have reduced unnecessary procedures and increased the efficiency of PCI and thereby led to a more favorable ICER than with medical therapy.

There were other differences between the COURAGE and the FAME 2 trials that may have affected the economic evaluation. In COURAGE, a significant proportion of patients had few, if any, angina symptoms, which may explain in part the smaller utility change after PCI documented in the COURAGE trial. The higher initial difference in cost of $11,410 between the PCI arm and the medical therapy arm in COURAGE compared with FAME 2 ($6027) was primarily attributable to the much lower initial cost assigned to the medical therapy arm in COURAGE (only $752 per patient) compared with FAME 2 ($3900 per patient). The cost of the PCI procedures in FAME 2 was also lower than in COURAGE, perhaps because fewer stents were used with PCI in the setting of an abnormal FFR. The more striking difference between studies is that the initial cost difference between PCI and medical therapy in COURAGE was essentially unchanged over 3 years of follow-up, despite a 40% reduction in the rate of subsequent coronary revascularization procedures among patients assigned to the PCI strategy. By contrast, in FAME 2, the initial difference in cost between PCI in the setting of an abnormal FFR and medical therapy narrowed over follow-up (Figure 1) because of a significantly higher rate of hospitalizations for acute coronary syndromes and for revascularization. The follow-up costs in the PCI arm of FAME 2 may have been further lowered compared with the PCI arm in COURAGE by the use of second-generation drug-eluting stents, which have had lower rates of restenosis than the bare-metal stents used in COURAGE.

The FAME 1 trial compared FFR-guided PCI with angiography-guided PCI, like that used in COURAGE, in patients with stable and unstable multivessel CAD. The economic evaluation of FAME 1 found that FFR-guided PCI led to improved clinical outcomes at lower costs (by $2000 per patient at 1 year) than angiography-guided PCI. In the FAME 2 trial, application of FFR guidance may have allowed for more judicious stenting in those patients with significant myocardial ischemia. By stenting only those lesions responsible for ischemia and medically treating the lesions that were not functionally significant, the benefit of PCI may have been maximized and the risks minimized.

The main limitation of the present study is that follow-up in FAME 2 was shorter than originally planned because of the premature discontinuation of the trial based on the recommendation of the Data and Safety Monitoring Board. As a result of the limited time horizon, we had to make a number of assumptions regarding the follow-up costs and durability of the benefit from PCI. The key assumption was that the initial benefit of PCI seen at 1 month would gradually diminish to zero over 3 years of follow-up. This assumption is based on the results of COURAGE and other studies in which the improvements in angina and quality of life from coronary revascularization declined over 3 years or more. The present results were similar, however, in various sensitivity analyses that varied the period of benefit between 1 and 4 years. Consequently, we believe that the projections of the durability of the benefit from PCI are reasonable. The early termination of the study may have also led to an overestimation of benefit by PCI. The other major limitation is that all patients in FAME 2 had FFR performed, so we cannot directly address the cost-effectiveness per se of using FFR. The initial FAME trial previously has shown the FFR-guided PCI strategy to have superior clinical outcomes and lower costs than standard, visually guided PCI.

**Conclusions**

In patients with symptomatic stable coronary artery disease, PCI in the setting of an abnormal FFR improves angina and quality of life and appears to be economically attractive compared with best medical therapy if one assumes that the benefit of PCI lasts longer than 1 year.

**Sources of Funding**

This study was sponsored by St. Jude Medical.

**Disclosures**

Dr Fearon receives institutional research support from St. Jude Medical. Drs Pijls and De Bruyne are consultants for St. Jude Medical. P. Jüni is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic, and Johnson & Johnson. CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronic, Boehrhringer Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisc, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 2 Trial randomized patients with stable coronary artery disease and at least 1 stenosis with an abnormal fractional flow reserve to either percutaneous coronary intervention (PCI) or medical therapy alone. Patients randomized to PCI had a significantly lower rate of hospitalization requiring urgent revascularization, with no difference in death or myocardial infarction. In this substudy of the FAME 2 Trial, we evaluate the economic and quality-of-life implications of performing PCI in patients with stable coronary artery disease and an abnormal fractional flow reserve. We found significantly higher costs in the PCI arm at baseline, primarily attributable to drug-eluting stents. During follow-up, the cost difference between the 2 groups narrowed significantly, primarily because of the increased costs in the medical therapy arm from revascularization. The PCI patients had an immediate and significant improvement in quality of life. Assuming the initial difference in utility between the 2 groups gradually narrowed over 3 years, and assuming the difference in costs at 1 year did not change, the incremental cost-effectiveness ratio of PCI was $36,000 per quality-adjusted life-year. These findings were robust in bootstrap replications and sensitivity analyses. PCI of coronary lesions with reduced fractional flow reserve improves outcomes and appears economically attractive compared with best medical therapy among patients with stable angina.

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_Circulation_. 2013;128:1335-1340; originally published online August 14, 2013; doi: 10.1161/CIRCULATIONAHA.113.003059

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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